Short cuts

What's new in the other general journals

Pelvic irradiation is linked to hip fracture in elderly women

CUMULATIVE INCIDENCE OF PELVIC FRACTURE IN ELDERLY WOMEN TREATED FOR CANCER

Radiotherapy for pelvic cancers is associated with hip fractures in elderly women, according to an observational study from the United States. The authors linked data from a national cancer database with data on Medicare claims for pelvic fractures among 6428 women aged >65. Women who had radiotherapy for cervical, rectal, or anal cancers were more likely to have a pelvic fracture subsequently than women with the same cancers who did not have radiotherapy (risk over 5 years, 14% *v* 8% for anal cancer, 8% *v* 6% for cervical cancer, and 11% *v* 9% for rectal cancer). Nine out of ten of these fractures were of the hip. The association was most obvious among women with anal cancers: radiotherapy increased their risk of hip fracture threefold (hazard ratio 3.16, 95% CI 1.48 to 6.73).

Although the researchers adjusted their analysis for other risk factors—including age, ethnic background, and stage of cancer—it's impossible to say for certain whether radiation alone was responsible for these differences in fracture rates. We don't know which of these women had other treatments such as chemotherapy, which might also affect bone metabolism, or oophorectomy, which certainly does.

Even so, it's likely that radiation is at least partly to blame for the extra fractures, and the researchers argue that women having radiotherapy for pelvic cancers should be told.

JAMA 2005;294:2587-93

Don't rely on history alone in patients with chest pain

Some kinds of pain are probably more serious than others in patients with chest pain. But a good description of the pain, though useful, is not powerful enough to identify patients who can be sent home safely, according to a systematic review. All it can do is raise or lower the index of suspicion.

For years doctors have been searching for a quick and easy way to distinguish between patients with and without cardiac chest pain. Failure to find one costs the US healthcare system an estimated \$8bn a year in unnecessary admissions. The best efforts so far have combined elements of the chest pain description with a patient's age, sex, and history of coronary artery disease. But none of these combined tools has been evaluated well enough to rely on in practice.

Until they are, the authors say a good history can still help doctors decide what other tests to order, and how quickly to order them. In studies, patients with pain that was stabbing, pleuritic, positional, or brought on by palpation were least likely to have an acute coronary syndrome. Patients with pain that was associated with exertion, or radiated to one or both arms or shoulders, were most likely to have serious cardiac disease.

JAMA 2005;294:2623-9

New drug for type 2 diabetes looks unsafe

In October of this year, the US Food and Drug Administration (FDA) agreed to license muraglitazar, a new drug for type 2 diabetes related to pioglitazone and rosiglitazone. US researchers, independent of the manufacturers, have since warned the FDA to withhold licensing after a re-analysis of data in the submission documents found worrying rates of cardiovascular events and death among people exposed to the drug.

The manufacturers, Bristol-Myers Squibb and Merck, submitted five trials of

muraglitazar to the FDA. Only one has been published. Researchers got the rest from the FDA's website, thanks to transparent US licensing procedures. In the new analysis combining data from all five trials, patients given muraglitazar were 2.2 times more likely to die or to have a non-fatal myocardial infarction or stroke than controls given a placebo or the comparator drug pioglitazone (95% CI 1.07 to 4.66). They were also 7.4 times more likely to develop congestive heart failure (95% CI 0.97 to 56.8).

The manufacturers' analysis of the same data had been somewhat different, and convinced the FDA that muraglitazar was safe. It might yet prove to be safe enough. But the authors of this new analysis and a linked editorial (pp 2633-5) agree that the findings should halt the licensing process pending a large safety trial. Clinical doses of muraglitazar have been tested in only 2374 patients so far, for a maximum of two years. Trial patients were relatively young (<55 years old on average) and relatively fit from a cardiovascular point of view. In practice, patients with diabetes tend to be older and sicker and need treatment for life.

JAMA 2005;294:2581-6

Patients with an ischaemic leg do equally well (or badly) after angioplasty or bypass surgery

MORTALITY AFTER BYPASS SURGERY OR BALLOON ANGIOPLASTY FOR LEG ISCHAEMIA

Surgeons debating the relative merits of angioplasty and bypass surgery for patients with a severely ischaemic leg finally have some reasonable evidence to support their opinions. In a randomised trial of 452 patients, long term outcomes were broadly similar after both kinds of treatment, although surgery caused more morbidity in the short term. Three years after their treatment, 57% of the 228 randomised to

surgery and 52% of the 224 randomised to angioplasty were still alive with their trial leg intact. Quality of life improved for patients in both groups, and mortality from all causes was about the same at the end of the trial.

All the trial patients had severe ischaemia and pain at rest. They also had the kind of disease that was amenable to either bypass or angioplasty. So they represent only a minority of patients presenting to hospitals with a severely ischaemic leg. They were elderly, 42% had diabetes, and four out of five were current or former smokers. A substantial minority had symptomatic coronary artery disease. Unsurprisingly, overall mortality was high.

Despite the poor state of these patients' arteries, only 58% were taking aspirin and only a third were taking a statin when they joined the trial. Improvements in medical management are clearly required, alongside the efforts of surgeons and radiologists.

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Timolol is a poor prophylactic against varices for people with cirrhosis

Non-selective β blockers such as timolol reduce portal venous pressure and prevent variceal bleeding in patients with gastroesophageal varices. So you might reasonably expect that the same non-selective β blockers would help prevent varices developing in the first place. Results from a recent randomised trial were disappointing, however. Unselected patients with liver cirrhosis and portal hypertension who took timolol were just as likely to develop varices as those who took a placebo (42/108, 39%, *v* 42/105, 40%). Worse, the timolol caused an excess of side effects (52/108, 48%, *v* 34/105, 32%; $P=0.02$). Seven patients taking timolol developed severe bradycardia, five had severe fatigue, and four became short of breath. The trial lasted five years.

A linked editorial (pp 2288-90) says the researchers may have selected the wrong patients (they had relatively mild portal hypertension) or the wrong drug (propranolol and nadolol cause fewer side effects). But in the end, the author concludes that this trial is sound enough to

stop doctors prescribing β blockers as primary prophylaxis against oesophageal varices. Attention should probably focus on monitoring their portal hypertension instead. In this trial, the patients least likely to get varices were those with a low baseline hepatic venous pressure gradient, and those whose gradient went down by at least 10% a year.

N Engl J Med 2005;353:2254-61

Fibrates for people with diabetes are good in theory, but unconvincing in practice

People with type 2 diabetes tend to develop a particular kind of dyslipidaemia—high serum concentrations of triglycerides, and low concentrations of high density lipoprotein cholesterol (the good one). As fibrates are good at correcting these particular abnormalities, they should in theory prevent cardiovascular disease in people with type 2 diabetes. This theory is reflected in management guidelines.

A large placebo controlled trial including 9795 people failed to find any convincing benefits, however. Over five years of treatment, fenofibrate was moderately good at preventing non-fatal heart attacks (hazard ratio 0.76, 95% CI 0.62 to 0.94; $P=0.01$), but had no significant impact on the likelihood of death from coronary heart disease (1.19, 0.90 to 1.57; $P=0.22$) or anything else (7.3% *v* 6.6%, $P=0.18$). In subgroup analyses, which should always be approached with caution, fenofibrate worked better for patients without cardiovascular disease at the start of the trial.

The authors find it hard to explain these rather mixed results, which are complicated by a greater use of statins in the placebo group (17% *v* 8%). But a linked editorial (pp 1829-1831) says it's now time to rethink guidelines that recommend fibrates for people with diabetes and a "typical" lipid profile.

Lancet 2005;366:1849-61

Sustained breast feeding is associated with lower risk of diabetes in US nurses

Breast feeding could help protect women from type 2 diabetes for up to 15 years, according to researchers from the United States. Data from two long running cohorts including 150 000 female nurses suggests that among parous women, each extra year they spend breast feeding reduces their risk of type 2 diabetes by about 15%.

The benefits of breast feeding were confined to women who had had their last baby less than 15 years before, and seemed independent of other risk factors for diabetes, including body mass index, family history of diabetes, and lifestyle indicators

such as diet, exercise, and smoking. Breast feeding did not protect women with gestational diabetes, perhaps because their underlying risk of diabetes is simply too high to respond to lifestyle changes. For other women, the benefits started to accrue after the first six months of breast feeding.

Female nurses are not particularly representative of other US women—they are better educated and more likely to breast feed. But in these women at least, sustained breast feeding seems to provide modest protection against diabetes.

JAMA 2005;294:2601-10

David Blaine had classic signs of refeeding syndrome after his long fast

When David Blaine, the illusionist and entertainer, finally came down from his glass box suspended over London, he had eaten nothing for 44 days. He had lost a quarter of his body weight so doctors from a teaching hospital nearby admitted him for observation, tests, and controlled refeeding.

The tests showed that at the end of his fast, David Blaine was dehydrated, deficient in vitamins B-1 and B-6, and a little low on potassium (serum concentration 3.3 mmol/l). His carbohydrate metabolism had survived unscathed, but he had a high serum concentration of free fatty acids and a very high serum concentration of hydroxybutyrate (4.92 mmol/l; compared with 0.163 mmol/l in controls fasted overnight). His liver function was slightly abnormal.

Doctors were most worried, however, by his serum concentration of phosphate, which was low on admission and fell even lower during the first 24 hours of refeeding. He needed an intravenous infusion of phosphate over the first night. Hypophosphataemia is a well known consequence of refeeding. So is oedema, which had occurred by day 10, despite restricting his salt intake. Blaine did not get hungry until three days after the end of his fast. Then he became very hungry.

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